Remarks

Claims 1-7, 20, 21, 46-91 are pending. Claims 1-4, 6, 20, 46, 70, 72-74, and 76-79 have been amended. Claims 84-91 have been newly added. Support for amended claim 1 can be found at least in original claims 1 and 2, on page 29, lines 1-5, on page 35, lines 25-29, and on page 85, lines 5-9. Claims 2, 3, and 46 were amended to be consistent with amended claim 1. Support for the exclusion of β-galactosidase from claims 1, 70, 72-74, and 76-79 can be found at least on page 85, lines 5-9. Support for the amendment to claim 4 can be found at least in original claim 6. Claim 6 was amended to be consistent with amended claim 4. Claim 20 was amended to be consistent with amended claims 1 and 2. Support for the recitation of "wherein the riboswitch regulates expression of the sequence" in claims 70 and 74 can be found at least in original claim 1. Support for the recitation of "wherein the riboswitch is derived from a naturally-occurring riboswitch" in claims 72, 73, 76, and 77 can be found at least in original claim 4.

Support for new claim 84 can be found at least in original claims 1 and 2 and from page 40, line 33, to page 41, line 4. Support for new claims 85 and 86 can be found on page 41, lines 6-9, and page 42, lines 7-9. New claim 87 is supported at least by page 39, lines 4-6. New claim 88 is supported at least by page 35, lines 28-29; from page 40, line 33, to page 41, line 2; page 41, lines 6-9; page 42, lines 7-9. Support for new claim 89 can be found on page 35, lines 28-29; from page 40, line 33, to page 41, line 2; page 41, lines 6-9; page 42, lines 7-9. Support for new claim 90 can be found at least in original claim 2, on page 29, lines 1-5, on page 35, lines 25-29, and on page 36, lines 27-33. Support for new claim 91 can be found at least in original claims 1 and 2 and from page 40, line 33, to page 41, line 4, and on page 36, lines 27-33.

Summary of Interviews

The undersigned representative of Applicants and Examiner Zara had a series of telephonic interviews for this application in March, April, and May 2009. The interviews all involved discussions of possible claim language that would overcome the standing art rejections and adequately define the riboswitch constructs. Applicants' representative and Examiner Zara discussed the Examiner's concerns about the interpretation of the term "coding region." The Examiner believed that "coding region" could be interpreted such that the then pending claims

were not distinguished from the cited art. Applicants' representative argued that "coding region" referred to a nucleic acid sequence that encoded amino acids.

Applicants' representative suggested that certain features of riboswitches also distinguished the claims from the prior art. These included that riboswitches regulate expression of genes via dynamic interplay between the aptamer domain and the expression platform domain of the riboswitch and that the expression platform domain of riboswitches changes state or structure when the aptamer domain changes state or structure upon binding a trigger molecule. The Examiner indicated that it would be clearer if these features were explicitly recited in the claims. Applicants' representative then prepared proposed claim language including recitation of some of these features and transmitted the proposed claim language on May 1, 2009 (the present amendment includes most of the proposed language). Applicants' representative and Examiner Zara discussed the proposed claim language and the Examiner indicated that the proposed language appeared to overcome the remaining issues, but that the Examiner would need to get supervisory approval.

Summary of Prosecution History

Before responding to the present rejections, Applicants would like to provide a brief summary on their understanding of how prosecution has gone. A non-final Office Action was mailed on December 22, 2006 with a written description rejection under 35 U.S.C. § 112, first paragraph, and a rejection under 35 U.S.C. § 102(a). Applicants submitted an amendment and response on April 26, 2007. A final Office Action was mailed on June 10, 2007 and maintained both the written description rejection under 35 U.S.C. § 112, first paragraph, and the rejection under 35 U.S.C. § 102(a). Applicants filed a notice of appeal on November 13, 2007 and filed an amendment and response on January 14, 2008. An Advisory Action was mailed on February 8, 2008 maintaining the rejections and stating that the amendment filed January 14, 2008 was not entered. Applicants then filed a Request for Continued Examination on May 13, 2008, along with an amendment and response to the June 10, 2007 Office Action and the February 8, 2008 Advisory Action. A non-final Office Action was mailed June 12, 2008. In the Office Action, the Examiner stated that "[a]pplicant's arguments, filed 5-13-08, in response to the rejections under 35 U.S.C. 112, first paragraph, have been fully considered and are persuasive. Therefore

the rejections have been withdrawn." This Office Action maintained the rejection under 35 U.S.C. § 102(a) and included a new rejection under 35 U.S.C § 112, second paragraph. Applicants filed an amendment and response on December 11, 2008.

At the Examiner's initiation, the undersigned representative of Applicants and Examiner Zara had a series of telephone interviews in March, April, and May 2009 to discuss the best way to quickly move this application towards issuance. Examiner Zara suggested possible amendments to the claims and Applicant's representative, in return, informally provided proposed claim language to the Examiner with the aim of identifying claim language that could be agreed on. This did not result in allowance of the application. Rather, the present non-final Office Action was mailed on May 19, 2009. The present Office Action includes a new written description rejection under 35 U.S.C. § 112, first paragraph, in which the examiner states that "[a]pplicant's arguments filed 5-13-08 have been fully considered but they are not persuasive." This statement contradicts the examiner's previous statement that Applicants' arguments in the May 13, 2008 response were persuasive (see June 12, 2008 Office Action).

Although applicants believe enough arguments and support have been provided in previous responses to overcome the written description rejection under 35 U.S.C. §112, first paragraph, and the examiner explicitly stated that the arguments were sufficient to overcome the rejection, applicants will again address this issue. It is not clear to Applicants that the new written description rejection under 35 U.S.C. § 112, first paragraph, has a different basis than the earlier written description rejection under 35 U.S.C. § 112, first paragraph, and so it is not clear why Applicants' arguments and evidence of record does not establish that there is adequate written description for the claimed constructs. Applicants would welcome the chance to discuss the rejections and the claims with the Examiner.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-7, 20, 21 and 46-83 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent it is applied to the claims as amended.

A.

The rejection acknowledges that the present application provides extensive description of examples of riboswitches, their structure, their operation, and, most significantly, the structural basis of their operation. Applicants submit that the description provided in the specification is clearly adequate to satisfy the written description requirement. The specification is replete with examples of structural features and sequence relationships of riboswitches. Importantly, the specification provides description of the key structural features and sequence relationships necessary for the operation of riboswitches in general, and provides multiple specific examples of such. For example, the specification (page 104, lines 13-20) states:

> Riboswitches that have been discovered are responsible for sensing metabolites that are critical for fundamental biochemical processes including adenosylcobalamin (AdoCbl) (see Example 1), thiamine pyrophosphate (TPP) (see Example 2), flavin mononucleotide (FMN), S-adenosylmethionine (SAM) (see Example 7), lysine (see Example 5) , guanine (see Example 6), and adenine (see Example 8). Upon interaction with the appropriate small molecule ligand, riboswitch mRNAs undergo a structural reorganization that results in the modulation of genes that they encode.

In each of the examples mentioned above, a detailed description of the riboswitch activated by a trigger molecule is given, along with an explicit discussion of how a trigger molecule interacts with the riboswitch. Thus, Applicants have described the general structure and operation of riboswitches; have identified the component parts of riboswitches, how they interconnect and operate, and how they can be recombined to form other riboswitches; and have provided a number of examples of riboswitches spanning a variety of genes and trigger molecules, thus solidifying both the validity of the general description and providing a representative number of examples of the structure of riboswitches. The numerous examples and consensus sequences provided clearly demonstrate Applicants' possession of the broad general subject matter of the present claims. It is hard to imagine how an applicant could provide more descriptive information of a pioneering invention than Applicants have provided.

Applicants note that riboswitches are made up of different domains that have different roles to play in the operation of the riboswitch. As fully described in the specification, riboswitches include an aptamer domain and an expression platform domain. The expression

platform domain of riboswitches generally involves alternative stem structures. The principles of operation and application of expression platform domains are described in the specification. The formation of hybridized stem structures in RNA is well known in the art, and the examples and principles of the structure and operation of platform domains of riboswitches is described in the specification. The structure-function relationship of the stem structures of expression platform domains is thoroughly described in the specification and provides all that is required by the written description requirement for this element of the claims.

Aptamer domains are essentially RNA aptamers. RNA aptamers in other contexts have been known and described for many years. The aptamer domains of riboswitches bind to trigger molecules and communicate through the RNA strand to the platform domain. Applicants submit that aptamers can be used and applied in riboswitches based on the description provided in the specification. Applicants discovered that aptamers in riboswitches are modular and can be used and interchanged between riboswitches. As noted in the specification, the aptamer domain of the riboswitch readily adopts the required structure without interference from, and independent of, the other control structures of riboswitches, even in aptamer domains synthesized *in vitro*:

> These conclusions are drawn from the observation that aptamer domains synthesized in vitro bind the appropriate ligand in the absence of the expression platform (see Examples 2, 3 and 6). Moreover, structural probing investigations suggest that the aptamer domain of most riboswitches adopts a particular secondary- and tertiary-structure fold when examined independently, that is essentially identical to the aptamer structure when examined in the context of the entire 5′ leader RNA. This implies that, in many cases, the aptamer domain is a modular unit that folds independently of the expression platform (see Examples 2, 3 and 6).

Specification, page 30, lines 23-30.

Therefore, the generic primary and secondary structural features of riboswitches described in the specification produce the necessary three-dimensional structure, without the need for guidance or further description. This is borne out by Applicants' description and analysis of guanine-responsive riboswitches and their structure. Having identified an example of an aptamer in a guanine-responsive riboswitch (where the aptamer binds to guanine and related compounds), Applicants searched for, found, and identified consensus elements of other guanine aptamers in guanine-responsive riboswitches in other genes (see part C of Figure 41). The

conservation and similarity of the primary sequence of aptamers in these riboswitches is strongly indicative that the higher level structure and aptamer function follow from the primary structure. Those of skill in the art would have been able to readily produce such functional riboswitches without concern for the three dimensional structure of the aptamer domain, because the three dimensional structure would have naturally folded into the correct orientation for functionality. Furthermore, as noted in the passage above, the aptamer domain can be a modular component that can be exchanged with other control sequences of the riboswitch. Because the aptamer domain can be exchanged with other control sequences, the riboswitch can comprise any aptamer. The specification comprises multiple examples of such aptamers (see, for example, Figures 11 and 41). Furthermore, aptamers in general are well known in the art and can be produced by known techniques, and are useful with the riboswitches disclosed in the specification.

Subsequent to Applicants' invention, it has been confirmed that the consensus primary and secondary structural elements described in the present application naturally produce the structure required for riboswitch function. Tertiary structures of five classes of riboswitches have been solved and published (guanine-, adenine-, TPP-, SAM-, and glucosamine-6-phosphate-responsive riboswitches). In each publication the authors note how well Applicants' models and probing data (which corresponds to the models and data described in the present application) fit with the tertiary structures. For example, Serganov et al., Chem. Biol. 11:1729-1741 (2004) (of record) describes the crystal structure of add adenine-responsive riboswitch and the xpt guanine-responsive riboswitch. The add and xpt riboswitches are examples of riboswitches in the present application (see, for example, Figures 11E, 11F, 23, 24, 25 28, 35 and Examples 6 and 8). Serganov (2004) compares the crystal structure, and the functional significance of the structure revealed, with the conserved primary and secondary structural elements that characterize the adenine and guanine riboswitches. See, for example, Serganov et al. (2004) page 1737, second column, third and fourth paragraphs; page 1738, fist column, first, second and third paragraphs; and page 1738, second column, first paragraph. Serganov et al. (2004) confirms and concludes that the primary and secondary structural information and the conserved elements of adenine- and guanine-responsive riboswitches that were earlier identified

have structural and functional significance in the crystal structure. For comparison to the crystal structure, a number of these passages in Serganov et al. (2004) refer to the primary and secondary structural information of citation number 24, Mandal & Breaker, Nature Struct. Mol. Biol. 11(1):29-35 (2004) (of record) which describes some of that same structural information in the present application. For example, present Example 8 describes work reported in Mandal & Breaker and Figures 35-40 in the present application correspond to Figures 1-6, respectively, in Mandal & Breaker. Thus, Serganov et al. (2004) provides evidence that the conserved and consensus structural elements identified in the present application are significant in determining the crystal structure of the riboswitch.

Serganov et al., Nature 441:1167-1171 (2006) (of record) describes the crystal structure of the thiM thiamine pyrophosphate (TPP) responsive riboswitch. The thiM TPP-responsive riboswitch is one of the example riboswitches in the present application (see, for example, Figures 6B, 9A, 11B, 13A, and 13B and Example 2). Serganov (2006) compares the crystal structure, and the functional significance of the structure revealed, with the conserved primary and secondary structural elements that characterize the TPP riboswitches. See, for example, Serganov et al. (2006) page 1167, first column, last paragraph; page 1168, second column first paragraph; page 1168, second column, last paragraph; and page 1169, first column, third paragraph. Serganov et al. confirms and concludes that the primary and secondary structural information and the conserved elements of TPP-responsive riboswitches that were earlier identified have structural and functional significance in the crystal structure. For comparison to the crystal structure, a number of these passages in Serganov et al. (2006) refer to the primary and secondary structural information of citation number 4, Winkler et al., Nature 419:952-956 (2002) (of record), which describes some of the same structural information in the present application. For example, present Example 2 describes work reported in Winkler et al. and Figures 6, 7, 8, 9A-C, and 13B in the present application correspond to Figures 1-5, respectively, in Winkler et al. Thus, Serganov et al. (2006) provides evidence that the conserved and consensus structural elements identified in the present application are significant in determining the crystal structure of the riboswitch.

A new class of riboswitch has also been identified based on the consensus primary and secondary structural elements describe in the present application, which confirms that riboswitch function predictably follows from the primary and secondary structural characteristics of the RNA. Kim et al., Proc. Natl. Acad. Sci. 104:16092-16097 (2007) (of record) describes the recently discovered 2'-deoxyguanosine-responsive riboswitch. The 2'-dG riboswitch was identified by searching sequences for primary and secondary structural elements based on the consensus structural elements of the guanine-responsive riboswitches that are described in the present application. In particular, Kim et al. refers to prior work with guanine- and adenine-responsive riboswitches as providing the basis of the identification of the new type of riboswitch, citing, for example, Mandal et al., Cell 113:577-586 (2003) (reference 26) (of record) and Mandal & Breaker, Nature Struct. Mol. Biol. 11(1):29-35 (2004) (reference 27) (of record). Example 6 in the present application describes work reported in Mandal et al. (2003) and Figures 23-29 in the present application correspond to Figures 1-7, respectively, in Mandal et al. (2003). As discussed above, present Example 8 describes work reported in Mandal & Breaker and Figures 35-40 in the present application correspond to Figures 1-6, respectively, in Mandal & Breaker. Once the 2'-dG riboswitch was identified in Kim et al. by these sequence and predicted secondary structural features, an example of a 2'-dG riboswitch was tested and determined to have the expected secondary structure and the expected riboswitch activity. Thus, Kim et al. also provides evidence that the consensus structural information provided in the present application represents structural information that adequately distinguishes the claimed riboswitches from other, non-riboswitch molecules. Further, the consistency of Applicants' description and understanding of riboswitch structure and function in the present application to subsequent findings regarding, and examples of, riboswitches is clear evidence that Applicants' were in possession of the riboswitches as presently claimed.

Applicants have also continued to identify additional riboswitches based on the original description and features described in the present application. Examples of such continued work include Barrick and Breaker, Genome Biology 8:R239 (2007), and Weinberg et al., Nucleic Acids Research 35(14):4809-4819 (2007) (of record). These publications show that the general description of a new class of regulatory element based in RNA provided in the present

application identified and described all of the key features and functions of riboswitches such that riboswitches could be identified and distinguished from what came before. Blount & Breaker, Nature Biotechnology 24(12):1558-1564 (2006), and Tucker & Breaker, Current Opinion in Structural Biology 15:342-348 (2005) (of record) are reviews that describe riboswitch structure and function. These publications show the consistency between the description provided in the present application and the continued in riboswitches since Applicants invention.

B.

Regarding the specific rationales presented in the rejection, Applicants make the following comments. The present rejection is based on three basic arguments:

1. that the specification allegedly does not point out (from among all the possible combinations) specific combinations of aptamers and expression platform domains that can function to regulate expression (page 4);
2. that the examples of riboswitches, their structures, and their structure function relationships described in the specification allegedly do not provide concise structural features required for the broad genus of constructs claimed (page 5);
3. that the specification allegedly provides only a means for screening for functional riboswitches rather than describing the riboswitches (page 5).

1.

The first argument appears to be improperly based on an enablement rationale. That is, this argument is based on the allegation that some combinations of aptamers and expression platform domains (and sequences to be regulated) would not function. Applicants first note that there is no evidence that some combinations of aptamer domains and expression platform domains will not function. As discussed at length above, Applicants have discovered the basic modular nature of riboswitches (aptamer operably linked to expression platform domain via alternative base paired stems), the basic operation of riboswitches (structural change of the aptamer when a trigger molecule binds is communicated to the expression platform domain via alterations in base pairing caused by the change in aptamer structure). Given this basic structure function relationship described in the specification and the numerous examples of riboswitches that embody this basic structure function relationship it is clear that Applicants have described

the core structural features and structure function relationship of riboswitches. Applicants submit that this is an example of exactly the type of situation the Federal Circuit had in mind when it refused to require complete and exact structural description of every claimed embodiment.

It appears that the rubric of "representative" examples of claimed subject matter used by the Federal Circuit is being applied in this rejection beyond the actual limited use it should have. It is clear that the written description requirement can be satisfied in at least three ways:[1]

a. the specification can include a complete structural description of all embodiments encompassed by the claims;
b. the specification can include a description of enough representative species to effectively describe the full scope of the claims;
c. the specification can provide a description of some structure and of the structure function relationship to allow those of skill in the art to arrive at the claimed embodiments.

The first option is trivial and rarely applies. The second is commonly applied in written description rejections (as it impliedly is applied here). The third option is a longstanding and often applicable standard for written description that is often overlooked in written description rejections.

Consider as an example the third option the case of the invention of an openable door. In this example, the inventor discovered that by attaching hinges to one edge of the cover of an opening and to one edge of the opening, the cover could be removed and replaced more efficiently and reliably. Assuming that a patent application for this invention described one specific example (a square door, two hinges), the principle of operation of this example, and a statement that the principle could be applied to doors of other shapes and with different numbers of hinges, there is no question that the inventor here would have provided sufficient written description for claims encompassing a wide variety of openable doors, the structures of most of which are not described in the specification. The reason why this is a sufficient written

[1] There are other ways than these to satisfy the written description requirement, but the three discussed here are sufficient to answer the rejection here.

description is that those of skill in the art would understand how to make and use all of those doors and can contemplate their structures. Further, those of skill in the art would understand from the specification that the inventor knew how to make and use all of the claimed doors and could contemplate their structures. This last is what the Federal Circuit and CCPA referred to as a description that shows the inventor was in "possession" of what is claimed. Not literal possession, but effective possession.

Although the example above involves a mechanical invention, the principle involved can also be validly applied to more complex inventions, including biotechnology inventions. An example of just such an application of this principle to a biotechnology invention can be seen in Amgen v. Hoechst, 314 F.3d 1313, 1332 (Fed. Cir. 2003). In Amgen, the claims of Amgen's patents referred to types of cells that can be used to produce recombinant human EPO. TKT (Amgen's opponent) argued that, because the Amgen patents did not describe the structure of the claimed cells, the patents failed to provide adequate written description of the claimed subject matter as required by Regents of the University of California v. Eli Lilly, 119 F.3d 1559 (Fed. Cir. 1997) and Enzo Biochem. v. Gen-Probe, 296 F.3d 1316 (Fed. Cir. 2002). The court in Amgen rejected this argument, holding that Amgen's claims, including the recited cells, were adequately described in Amgen's patents. The court noted that unlike in Eli Lilly or Enzo

> the claim terms at issue here [in Amgen] are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend....This difference alone sufficiently distinguishes Eli Lilly, because when used, as here, merely to identify types of cells (instead of undescribed, previously unknown DNA sequences), the words 'vertebrate' and 'mammalian' readily 'convey distinguishing information concerning [their] identity' such that one of ordinary skill in the art could 'visualize or recognize the identify of the members of the genus.'

Amgen at 1332. Clearly Amgen did not provide anything close to a written description of the structure of the mammalian cells used in the claims, of the exact structure of the combination of the cells and the recombinant gene being used, nor of the structural and functional relationships between the recombinant gene and the expression machinery of the mammalian cell that was required to have the gene expressed. Just as in the example of the openable door, the court in Amgen accepted that neither a complete structural description nor a complete description of all

the structure function relationships involved was required in order for an adequate written description to be present. Rather, Amgen was allowed to rely on the general description of mammalian cells combined with the knowledge that those of skill in the art knew what they were and how to use them. Significantly, Amgen provided the principles for using undescribed mammalian cells combined in undescribed ways with recombinant genes to produce the claimed recombinant cells. Because the principles of these combinations were described in the application there (or known to those of skill in the art), the court in Amgen considered that Amgen demonstrated "possession" of the full scope of the claimed recombinant mammalian cells. This is the same principle of written description at work in the example of the openable door, and is the same principle of written description that Applicants have thoroughly and extensively satisfied with the present application and claims.

This principle is also supported by Capon v. Eshhar v. Dudas, 76 USPQ2d 1078, 1082 (Fed. Cir. 2005). In Capon the court held that neither a complete nucleotide description nor operability of every permutation within a generally operable invention is required in order for an adequate written description of generically claimed nucleic acid constructs. Capon involved claims broadly drawn to nucleic acid constructs encoding a chimera of single-chain variable portions of antibodies and transmembrane lymphocyte signaling proteins. Both parties in an interference proceeding had appealed a decision by the Board of Patent Appeals and Interferences ("Board") that their specifications failed to provide an adequate written description of the claimed constructs. In particular, the Board stated that it could not be known whether all the permutations and combinations covered by the claims would be effective for the intended purpose, and that the claims were too broad because they might include inoperative species. Specifically, the Board stated that the disclosure of specific examples provided in each party's specification, in the absence of any sequence information within the specification, did not provide adequate written descriptive support for the invention. In reversing the Board's decision, the court in Capon held that since specific examples of the production of specified chimeric genes were provided in the specification, it was not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim. The court also confirmed its long-standing precedent that the disclosure required to meet the written

description requirement will vary with the nature and scope of the invention. In sum, the court in Capon concluded that knowledge in the art of the sequences of the nucleic acids that were joined to construct the chimeric DNA molecules, together with Appellants' disclosures of known methods for joining nucleic acid molecules to form chimeric DNAs, provided adequate written description of DNA molecules encoding chimeric receptors, and therefore recitation of exact nucleotide sequences was not required.

Applicants assert that this same logic applies to the claimed riboswitch constructs. Applicants have described the general structure and operation of riboswitches; have identified the component parts of riboswitches, how they interconnect and operate, how they can be recombined to form other riboswitches; and have provided a number of examples of riboswitches spanning a variety of genes and trigger molecules. Like the Appellants' disclosures in Capon, Applicants have provided specific examples of riboswitches, as well as clear guidance of how to select the modular components thereof, such as the aptamer. Like the components of the chimeric DNAs in Capon, extensive sequence information is available for the claimed riboswitch components.

As with the Board's basis for alleged unpatentability in Capon, the present rejection is based on an allegation that some of the presented riboswitch sequences would not be functional. As stated by the court in Capon, it is not necessary that every permutation be effective in order for an inventor to obtain a generic claim, provided that the effect was sufficiently demonstrated to characterize the invention. This principle applies to the present invention and facts with equal force and effect. Applicants submit that riboswitches were well demonstrated in the specification, as evidenced by the lengthy discussion of riboswitches therein (see page 104, lines 13-20, and the examples referenced in this passage, for example; see also the discussion above). Applicants have provided a variety of example riboswitches (and riboswitch components) and have identified consensus sequences for a number of riboswitches, which clearly qualifies as concise structural features that define the riboswitches and their components.

The rejection alleges that the examples given, and the generic description of riboswitches, comprising an aptamer domain and an expression platform, the generic descriptions of structure function relationships for some identified (and proposed) stem structures of platform domains,

and the sequence comparisons between previously described riboswitches found in nature, and sequence databases, together do not provide the concise structural features required for the very broad genus of compounds claimed. Applicants first note again that, as in Capon, the recitation of exact nucleotide sequences is not required for every permutation and combination of the claimed constructs. Applicants also note that, as discussed extensively above, the present specification provides a significant amount of information, including both specific and generic sequences, for myriad riboswitches. It is not seen how this fails to provide the "concise structural features" required by the rejection. On the contrary, the rejection merely concludes without evidence or sufficient reasoning that the extensive structural information provided is inadequate. It can only be concluded that the rejection is applying a per se requirement of a type rejected by the court in Capon for a certain quality of written description. Such a per se and unsupported requirement is not supported by either the statute or the caselaw. Applicants have provided a full and complete disclosure, commensurate with knowledge that comprises the state of the art. One of skill in the art would have been able to identify riboswitches, and the components thereof, needed to make the claimed constructs, based on the disclosure in the specification.

Furthermore, in Falkner v. Inglis, 79 USPQ2d 1001 (Fed. Cir. 2006), the Federal Circuit found that Applicant need not spell out every detail of an invention, but only enough to convince a person of skill in the art that the inventor possessed the invention. At issue in Falkner were claims to a poxvirus lacking essential genes, for use as a vaccine. Although the specification at issue in Falkner neither identified, nor provided the sequence of, any essential poxvirus gene, essential regions of poxvirus were known in the art. The court, upholding a Board decision, found that the claims were adequately described. In support of its decision, the court held that:

> (1) examples are not necessary to support the adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.

Although the specification at issue in Falkner neither identified, nor provided the sequence of, any essential poxvirus gene, essential regions of poxvirus were known in the art.

The court agreed that those of skill in the art could easily select essential poxvirus genes. This is significant for the present rejection. The rejection dismisses Applicants' argument that those of skill in the art could readily produce the claimed constructs based on Applicants disclosure. The rejection discounts this argument on the basis that Applicant must be in possession at the time of filing of an adequate representation of species for the broad genus of compounds claimed, not merely have the ability to screen for such peptides. However, it is clear from Falkner that "possession" for written description purposes does not require actual possession (i.e., reduction to practice) nor even a structural description of all elements of an invention. The specification at issue in Falkner did not describe any "essential genes" of any poxvirus, nor provide specific guidance for which genes of poxvirus were or were not essential. Nevertheless, the court in Falkner held that such specific description was not required to satisfy the written description requirement. Significantly, the court recognized that the fact that those of skill in the art could identify essential poxvirus genes (an identification found nowhere in the specification at issue in Falkner) was sufficient to satisfy the written description requirement. This is analogous to the present constructs where those of skill in the art could easily identify the claimed riboswitches by reference to Applicants' extensive disclosure. As a result, the present application satisfies the written description requirement for the present claims.

Although one can imagine changes and combinations of aptamers and expression platform domains that would not work, those of skill in the art would know to avoid these (and the present specification provides the information that allows such avoidance). The very fact that such non-functional examples can be envisioned indicates that their nature would not be mysterious or unknown to those of skill in the art. For example, the specification includes a number of alterations to riboswitches that predictably caused the riboswitches to become non-functional (by changing nucleotides involved in functionally critical base pairs, for example; see Examples). This is clear evidence that Applicants have provided sufficient description of the design principles of riboswitches to allow those of skill in the art to make all of the claimed riboswitches and to show that Applicants had possession of the broad class of riboswitch constructs claimed. Further, even if it were the case that the claims encompassed some

nonfunctional riboswitches, the written description requirement does not require that all such embodiments be excluded form the claims.

2.

The second argument apparent in the rejection that was listed above (that the examples of riboswitches, their structures, and their structure function relationships described in the specification allegedly do not provide concise structural features required for the broad genus of constructs claimed) also fails for similar reasons. First, the rejection fails to provide any evidence or reasons why the example riboswitch structures, the principles of their operation, the modular nature of the riboswitches and the genes they regulate, and the principles of combining different riboswitch elements, all of which are described in the specification, leave doubt about the application of this description to arrive at the claimed constructs. All that this portion of the rejection provides is unsupported allegations that the specification "fails to provide a representative number of species" and does "not provide the concise structural features required" to satisfy the written description requirement. Such reasoning does not establish a *prima facie* case of lack of written description.

Regarding "representative number of species," Applicants first submit that it is not required that a representative number of species be provided if an adequate written description is provided in other ways. As discussed above, it is perfectly adequate to provide written description by providing example structures along with principles of structure function relationships that can be used to arrive at the claimed subject matter. Applicants also submit the principle of a "representative number of species" established by the Federal Circuit actually embodies the means by which Applicants have provided an adequate written description here. The rationale behind the Federal Circuit's "representative number of species" principle is in part that examples of embodiments can paint a picture of the genus of embodiments that those of skill in the art can fill in and envision. This is what Applicants have provided here. Applicants also submit that the example riboswitches, aptamer domains, and expression platform domains described in the specification are representative of the claimed riboswitches. The present rejection does not provide any evidence that the examples in the specification are not representative of the claimed genus of riboswitches. Applicants must emphasize that merely

asserting that the claims encompass many combinations and then concluding that the description provided does not constitute a "representative number of species" or does "not provide the concise structural features required" does not establish a *prima facie* case of lack of written description.

3.

The third argument apparent in the rejection that was listed above (that the specification allegedly provides only a means for screening for functional riboswitches rather than describing the riboswitches) might be a problem if the specification otherwise had an inadequate written description. As demonstrated above, however, the specification provides a sufficiently complete, and completely acceptable, written description of the claimed constructs. Given this, it cannot be said that written description for the claimed constructs relies on screening as the written description. Because of this, the third argument is not relevant to the present claims and does not establish that written description is lacking for the claimed constructs.

For all of the above reasons, Applicants submit that the specification provides and adequate written description of the claimed constructs. Applicants hereby request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 102

A. Claims 1-7, 20, 21, 46-58, 70-83 were rejected under 35 U.S.C. § 102(a) as being anticipated by Nahvi et al. Applicants respectfully traverse this rejection to the extent it is applied to the claims as amended

Nahvi et al. discloses an adenosylcobalamin-responsive riboswitch coupled to a sequence encoding β-galactosidase.

For a rejection of claims to be properly founded under 35 USC §102, it must be established that a prior art reference discloses each and every element of the claims. Hybritech Inc v Monoclonal Antibodies Inc, 231 USPQ 81 (Fed. Cir. 1986), cert. denied, 480 US 947 (1987); Scripps Clinic & Research Found v Genentech Inc, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in Scripps, 18 USPQ2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . *There must be no difference*

between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

Claims 1, 70, 72-74, and 76-79 have been amended to recite "wherein the sequence does not encode β-galactosidase" or "wherein the coding region does not encode β-galactosidase." Claims 1-3, 20, 21, 46-58, 72, 73, and 76-83 require, and claims 70 and 74 have been amended to require, that the riboswitch regulate expression of a sequence. Claims 1-3, 20, 21, 46-58, and 70-83 all require that the riboswitch be heterologous to the sequence in the construct. Because the only constructs disclosed by Nahvi et al. in which a riboswitch regulates expression of a heterologous sequence are constructs encoding β-galactosidase, Nahvi et al. fails to disclose every element of claims 1-3, 20, 21, 46-58, and 70-83. For at least this reason, Nahvi et al. fails to anticipate claims 1-3, 20, 21, 46-58, and 70-83.

Claim 4 requires a riboswitch that is a non-natural derivative of a naturally-occurring riboswitch and has been amended to recite "wherein the riboswitch is not derived from a naturally-occurring adenosylcobalamin-responsive riboswitch." Because the only constructs disclosed by Nahvi et al. having a non-natural derivative of a naturally-occurring riboswitch include a riboswitch derived from a naturally-occurring adenosylcobalamin-responsive riboswitch, Nahvi et al. fails to disclose every element of claims 4-7. For at least this reason, Nahvi et al. fails to anticipate claims 4-7.

Thus, Nahvi et al. fails to anticipate any of claims 1-7, 20, 21, 46-58, and 70-83. Withdrawal of the rejection is respectfully requested.

Applicants also note that new claims 84-91 all require that the riboswitch regulate expression of a sequence, that the riboswitch be heterologous to the sequence or that the riboswitch be internally heterologous, and that the sequence does not encode β-galactosidase.

B. Claims 1, 2, 4, 5, 7, 20, 21, 46 and 70-83 were rejected under 35 U.S.C. § 102(b) as being anticipated by Werstuck et al. Applicants respectfully traverse this rejection to the extent it is applied to the claims as amended.

Werstuck et al. discloses constructs with artificial aptamers inserted in the 5' noncoding region of a gene where binding of a small molecule to the aptamer blocks expression of the gene.

For a rejection of claims to be properly founded under 35 USC §102, it must be established that a prior art reference discloses each and every element of the claims. Hybritech Inc v Monoclonal Antibodies Inc, 231 USPQ 81 (Fed. Cir. 1986); Scripps Clinic & Research Found v Genentech Inc, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in Scripps, 18 USPQ2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

Claims 5, 70, 71, 74, 75, and 78 require, and claim 1 has been amended to require, that the riboswitch comprise an expression platform domain. As described in the present application, the expression platform domain of a riboswitch dynamically interacts with the aptamer domain of the riboswitch to result in regulation of expression (see page 35, lines 24-29). Claim 1 has also been amended to require that the riboswitch regulate expression of the sequence via dynamic interplay between the aptamer domain and the expression platform domain. Because Werstuck et al. fails to disclose any expression platform domain (the Werstuck et al constructs include only aptamers) and fails to disclose alteration of the structure of the construct that affects expression, Werstuck et al. fails to disclose every feature of claims 1, 2, 5, 20, 21, 46, and 70-83. For at least this reason, Werstuck et al. fails to anticipate claims 1, 2, 5, 20, 21, 46, and 70-83. Withdrawal of the rejection is respectfully requested.

Claims 4, 5, and 7 require that the riboswitch be a non-natural derivative of a naturally-occurring riboswitch. Because Werstuck et al. does not disclose any naturally-occurring riboswitch or any derivative of a naturally-occurring riboswitch (Werstuck et al. only discloses artificial aptamers), Werstuck et al. fails to disclosed every feature of claims 4, 5, and 7. For at least this reason, Werstuck et al. fails to anticipate claims 4, 5, and 7. Withdrawal of the rejection is respectfully requested.

Applicants also note that new claims 84-91 all require that the riboswitch include an expression platform domain and either a change in the structure of the expression platform domain when the aptamer domain is bound by a trigger molecule or regulation of expression via dynamic interplay between the aptamer domain and the expression platform domain.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A deposit order account charge made electronically in the amount of $1093.00, representing $555.00 for the fee for a small entity under 37 C.F.R. § 1.17(a)(3), $208.00 for the fee for a small entity under 37 C.F.R. § 1.16(i), and $330.00 for the fee for a small entity under 37 C.F.R. § 1.16(h), and a Request For Extension Of Time are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-4667.

Respectfully submitted,

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